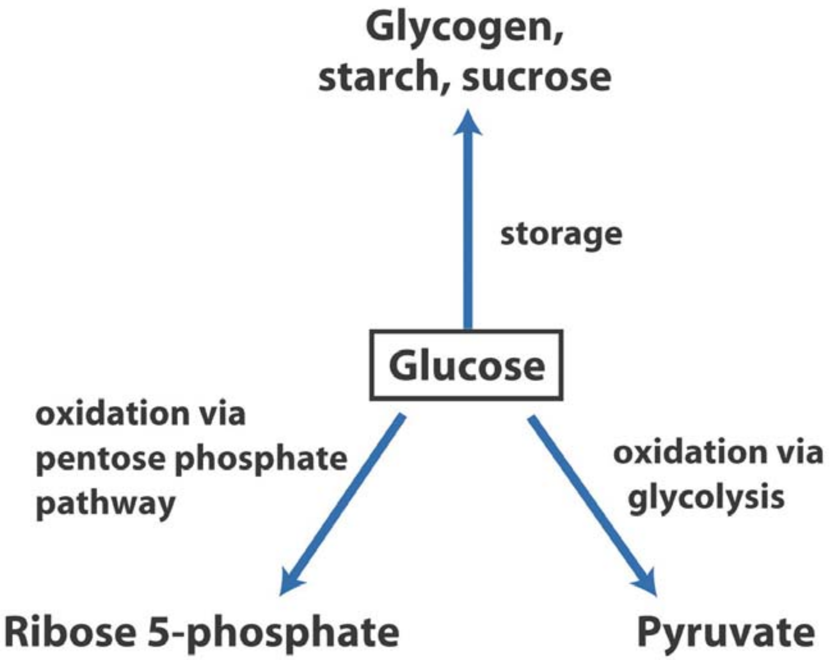
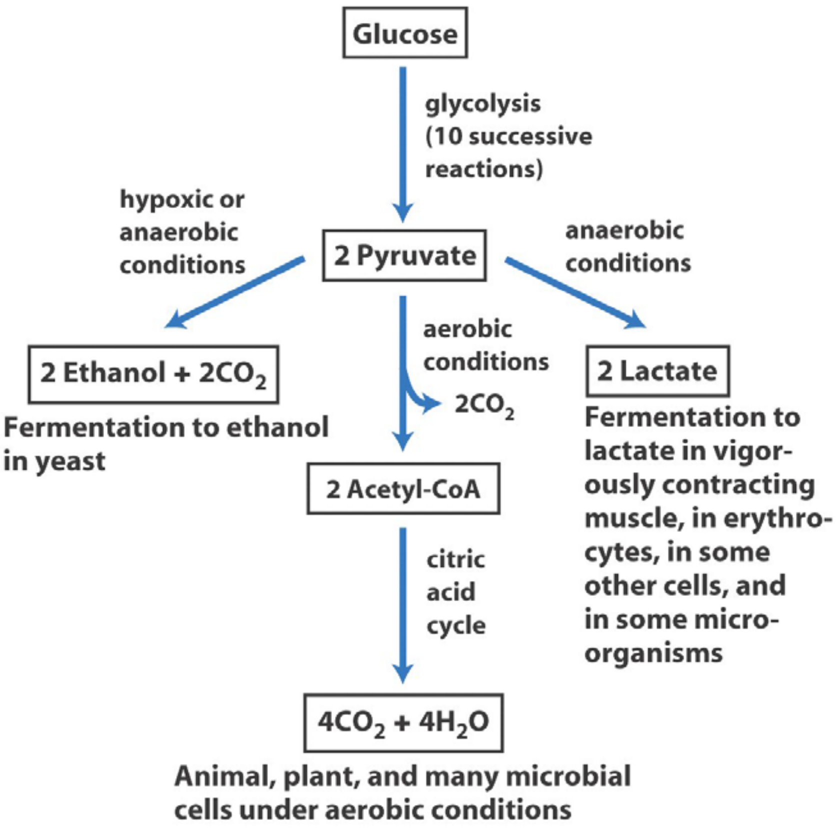
Glycolysis

- Introduction: Glucose utilization
- Glycolysis
- Entry of glucose into the cell
- Preparatory phase of glycolysis
- Energy production



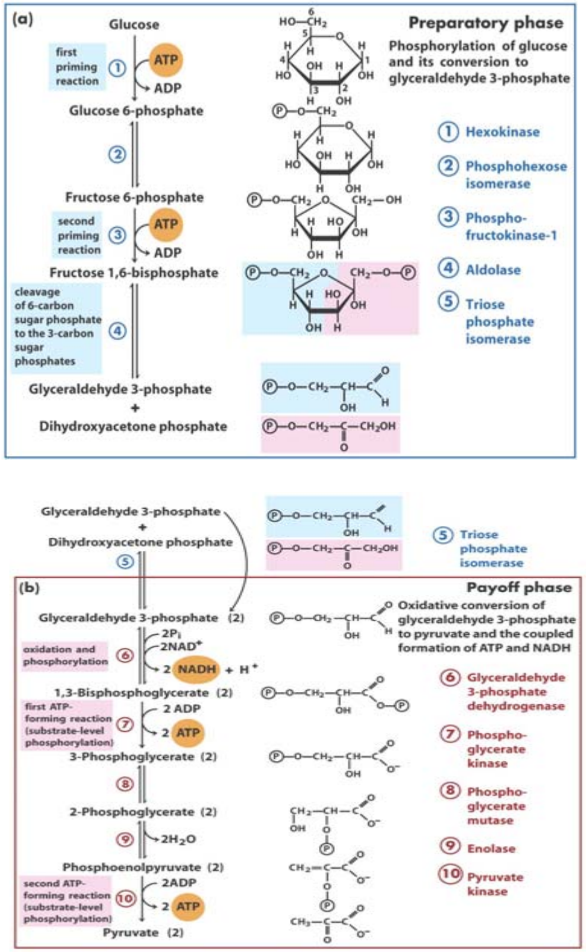
Glycolysis
Embden-Meyerhoff pathway

- Introduction
- Glycolysis
- Entry of glucose into the cell
- Preparatory phase of glycolysis
- Energy production



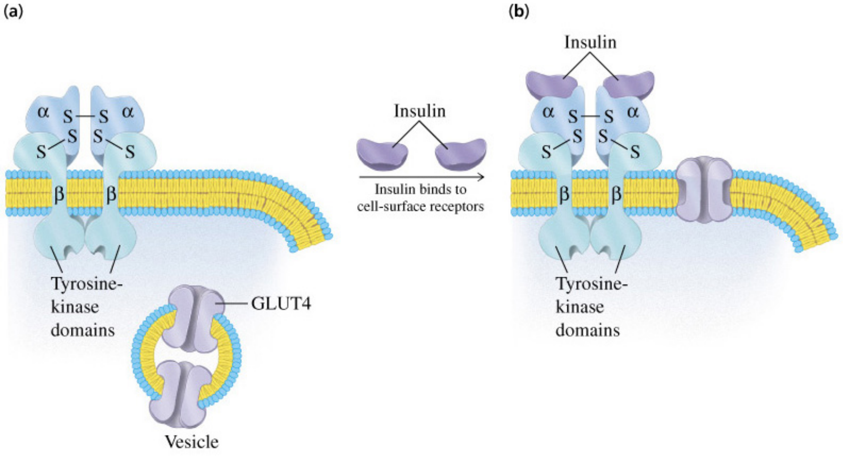
Glycolysis

- Ancient Pathway
- In cytoplasm
- No oxygen required
- Used for energy production
- Production of intermediates for other pathways
- Found in tissues with limited blood supply



Entry of glucose into the cell

- Transport
- hexokinase
- glucokinase in liver
- hexokinase vs glucokinase
- forms anion to keep in cell

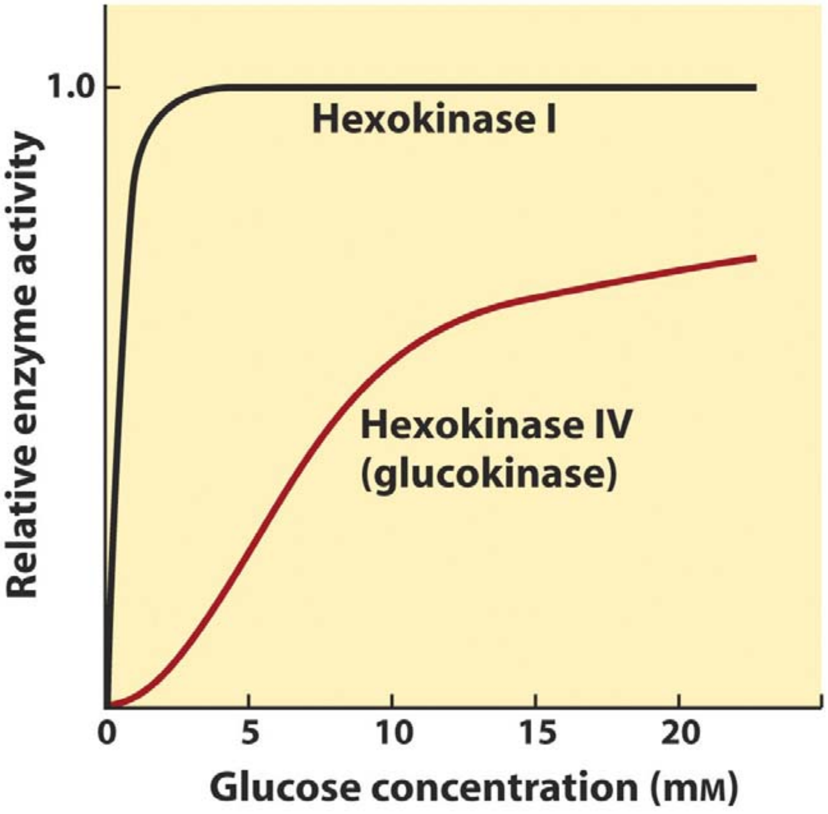


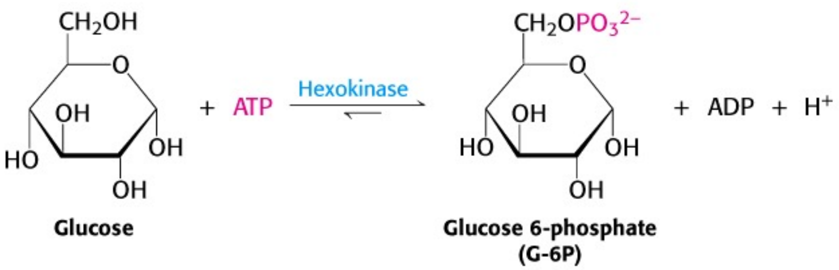
Glucose Transporters

TABLE 16.4 Family of glucose transporters

Name	Tissue location	K_m	Comments
GLUT1	All mammalian tissues	1 mM	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15–20 mM	In the pancreas, plays a role in regulation of insulin In the liver, removes excess glucose from the blood
GLUT3	All mammalian tissues	1 mM	Basal glucose uptake
GLUT4	Muscle and fat cells	5 mM	Amount in muscle plasma membrane increases with endurance training
GLUT5	Small intestine	—	Primarily a fructose transporter

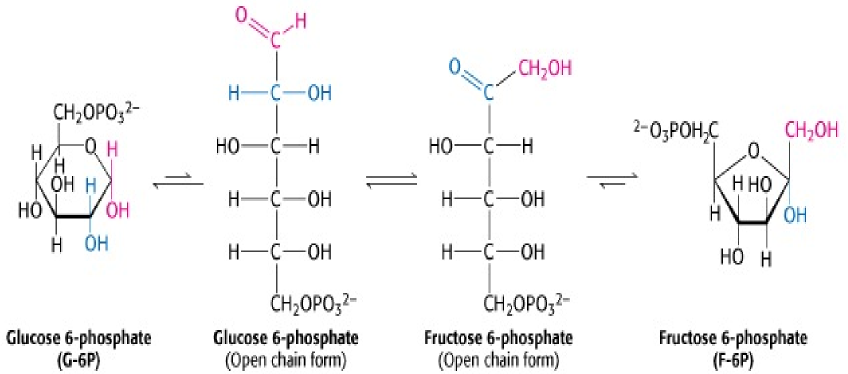
Kinetic properties of hexokinase

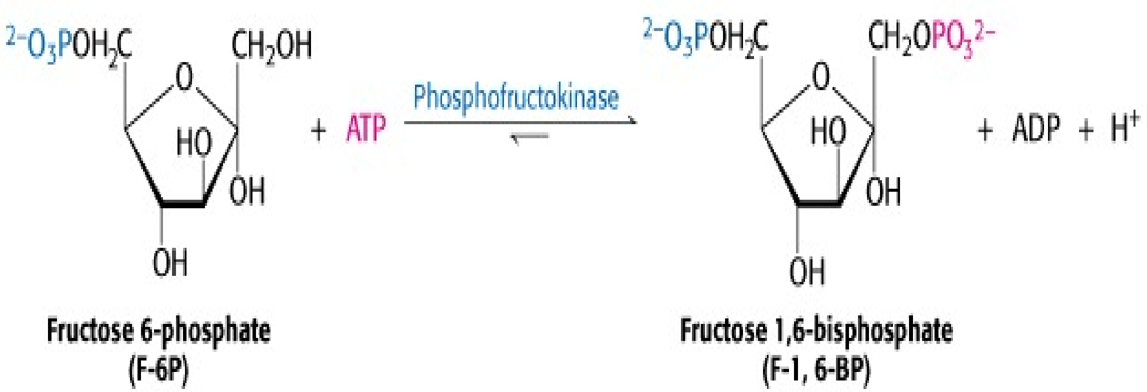




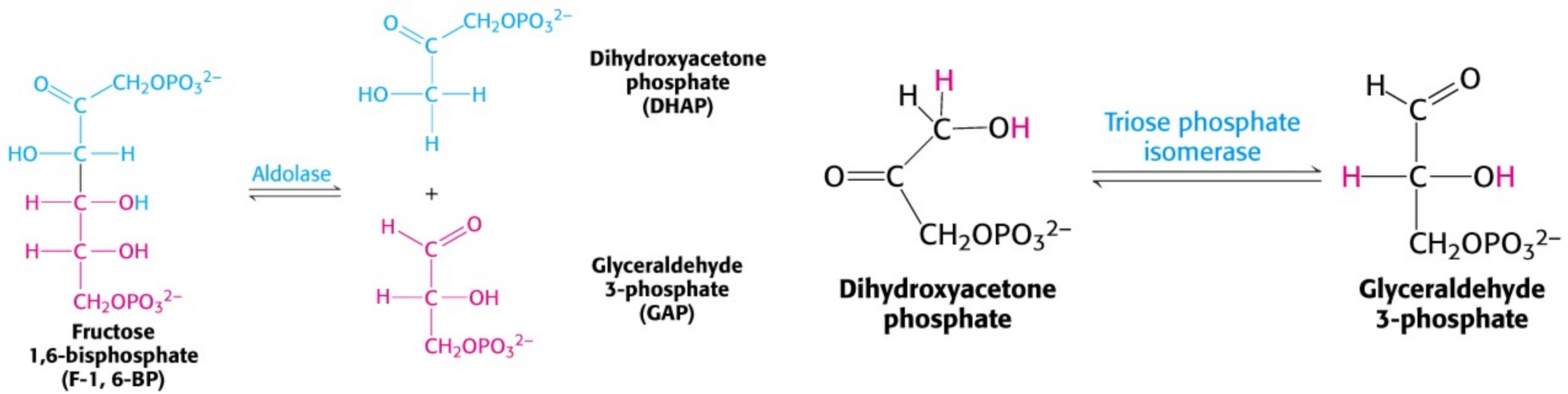
Preparatory phase of glycolysis

- 2 ATP
- Phosphofructokinase (PFK-1)
- regulated
- allosterically



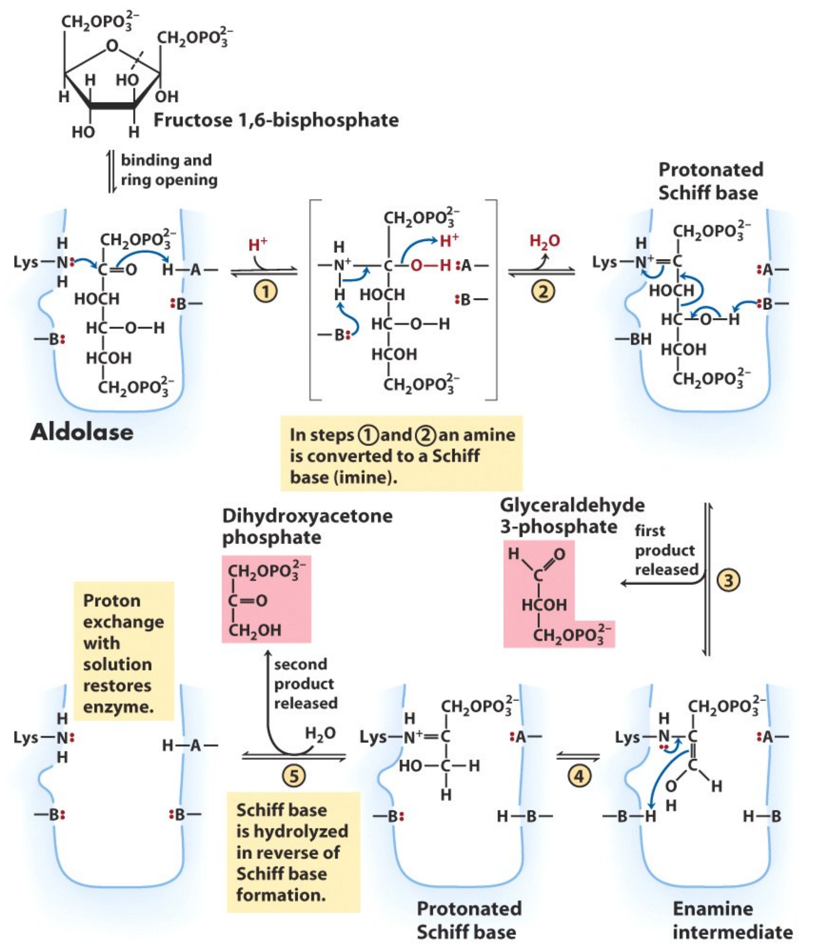


Aldolase


Aldolase
Dihydroxyacetone phosphate (DHAP)
Glyceraldehyde 3-phosphate (GAP)
Fructose 1,6-bisphosphate (F-1, 6-BP)
Triose phosphate isomerase
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate

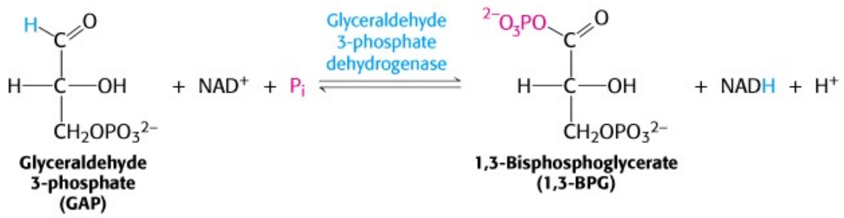
Mechanism: Aldolase

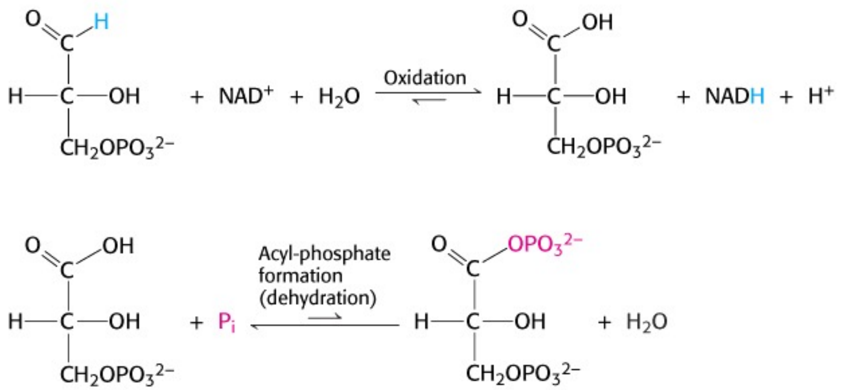
- **Nucleophillic (electron rich group attacks electron deficient nucleus attack on #2 carbon.**
- **Lysine residue forms a Schiff base**
- **OH (from C) and H from cysteine form H_2O.**
- **Thiolate gets H^+ from substrate, release Gly 3-P**
- **His residue donates H^+**
- **Hydrolysis of Schiff base**



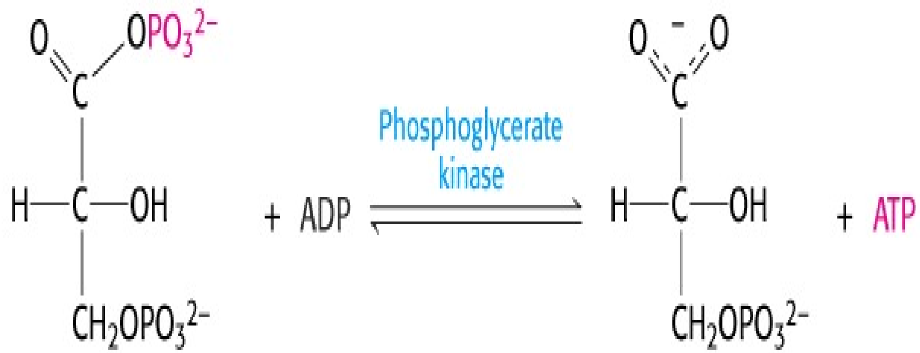
Energy production

- 1,3 BPGA
- PEP
- 4 ATP & 2 NADH
- Pyruvate end product



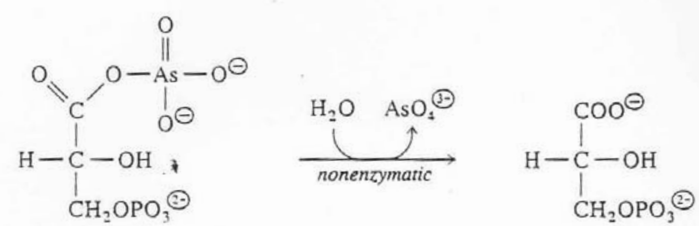


Phosphoglycerate Kinase



1,3-Bisphosphoglycerate 3-Phosphoglycerate

Effect of aresenate

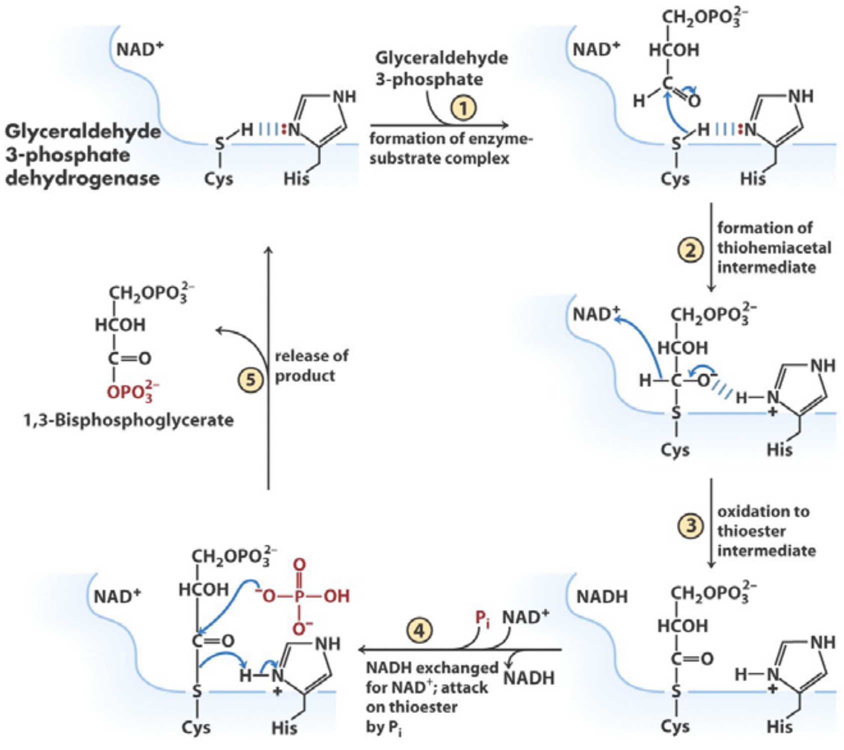


1-Arseno-3-phosphoglycerate 3-Phosphoglycerate

(Figure 12·14). This nonenzymatic hydrolysis produces 3-phosphoglycerate and regenerates inorganic arsenate, which can again react with a thioacyl-enzyme intermediate. Glycolysis can proceed from 3-phosphoglycerate, but the ATP-producing reaction involving 1,3-*bis*phosphoglycerate is bypassed. As a result, there is no net formation of ATP from glycolysis, with potentially lethal consequences.

Mechanism: dehydrogenase

- **Ionized cysteine attacks C-1, forming thiohemiacetal (aldehyde/thio group)**
- **Hydride ion (H^-) reduces NAD^+, forms thioacyl intermediate**
- **Phosphate enters displaces thioacyl**
- **1,3 Bisphsopho disassociates.**



PEP to Pyruvate

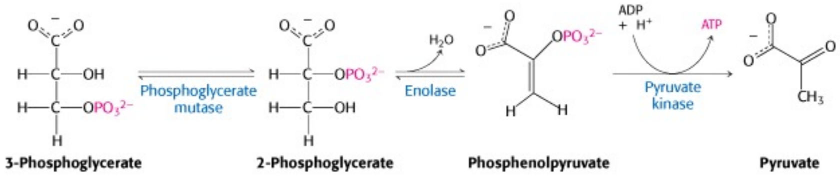
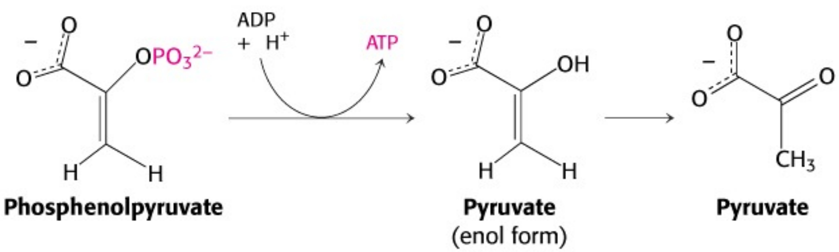


Table 15-1
Consumption and generation of ATP in glycolysis

Reaction	ATP change per glucose
Glucose ⟶ glucose 6-phosphate	−1
Fructose 6-phosphate ⟶ fructose 1,6-bisphosphate	−1
2 1,3-Bisphosphoglycerate ⟶ 2 3-phosphoglycerate	+2
2 Phosphoenolpyruvate ⟶ 2 pyruvate	+2
Net	+2



ENERGY YIELD IN THE CONVERSION OF GLUCOSE INTO PYRUVATE

The net reaction in the transformation of glucose into pyruvate is

$$\text{Glucose} + 2\ P_i + 2\ \text{ADP} + 2\ \text{NAD}^+ \longrightarrow 2\ \text{pyruvate} + 2\ \text{ATP} + 2\ \text{NADH} + 2\ H^+ + 2\ H_2$$

Biological Systems

- **Net 2 ATP**
- **2 NADH**
- **Most reactions at equilibrium can be reversed**

Table 15-3.
Typical concentrations of glycolytic intermediates in erythrocytes

Intermediate	μM
Glucose	5000
Glucose 6-phosphate	83
Fructose 6-phosphate	14
Fructose 1,6-bisphosphate	31
Dihydroxyacetone phosphate	138
Glyceraldehyde 3-phosphate	19
1,3-Bisphosphoglycerate	1
2,3-Bisphosphoglycerate	4000
3-Phosphoglycerate	118
2-Phosphoglycerate	30
Phosphoenolpyruvate	23
Pyruvate	51
Lactate	2900
ATP	1850
ADP	138
P_i	1000

After S. Minakami and H. Yoshikawa, *Biochem. Biophys. Res. Comm.* 18(1965):345.

Overall reactions of glycolysis

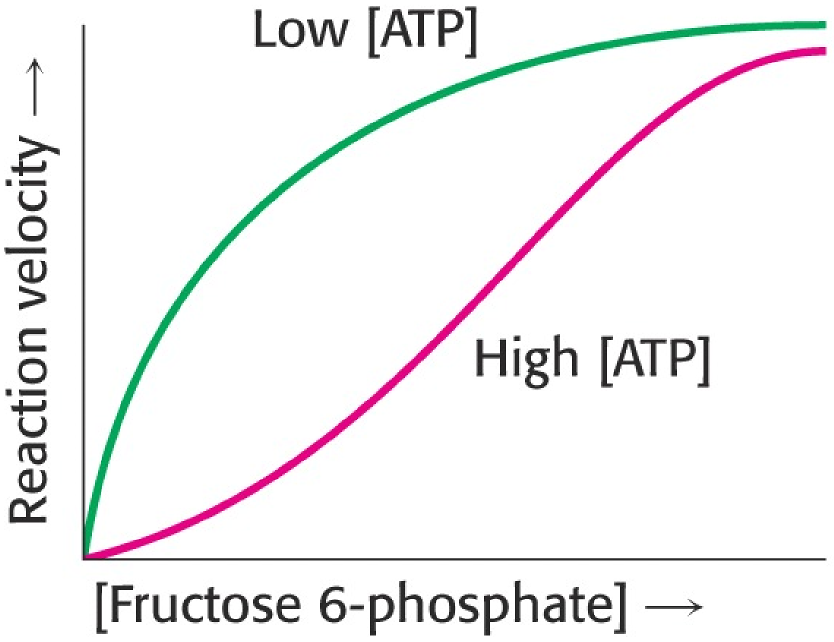
TABLE 14–2 **Free-Energy Changes of Glycolytic Reactions in Erythrocytes**

Glycolytic reaction step	$\Delta G'^{\circ}$ *(kJ/mol)*	ΔG *(kJ/mol)*
① Glucose + ATP ⟶ glucose 6-phosphate + ADP	−16.7	−33.4
② Glucose 6-phosphate ⇌ fructose 6-phosphate	1.7	0 to 25
③ Fructose 6-phosphate + ATP ⟶ fructose 1,6-bisphosphate + ADP	−14.2	−22.2
④ Fructose 1,6-bisphosphate ⇌ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate	23.8	0 to −6
⑤ Dihydroxyacetone phosphate ⇌ glyceraldehyde 3-phosphate	7.5	0 to 4
⑥ Glyceraldehyde 3-phosphate + P_i + NAD^+ ⇌ 1,3-bisphosphoglycerate + NADH + H^+	6.3	−2 to 2
⑦ 1,3-Bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP	−18.8	0 to 2
⑧ 3-Phosphoglycerate ⇌ 2-phosphoglycerate	4.4	0 to 0.8
⑨ 2-Phosphoglycerate ⇌ phosphoenolpyruvate + H_2O	7.5	0 to 3.3
⑩ Phosphoenolpyruvate + ADP ⟶ pyruvate + ATP	−31.4	−16.7

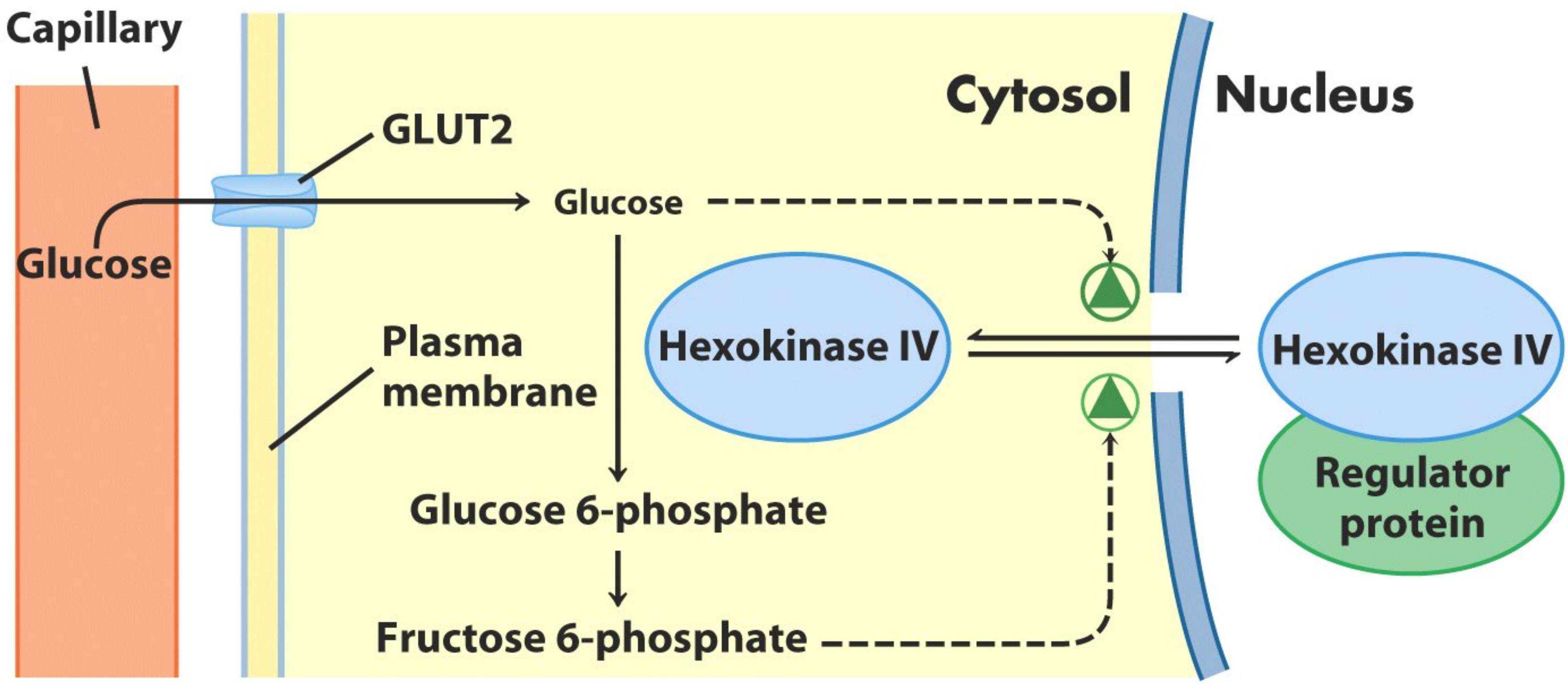
Note: $\Delta G'^{\circ}$ is the standard free-energy change, as defined in Chapter 13 (p. 491). ΔG is the free-energy change calculated from the actual concentrations of glycolytic intermediates present under physiological conditions in erythrocytes, at pH 7. The glycolytic reactions bypassed in gluconeogenesis are shown in red. Biochemical equations are not necessarily balanced for H or charge (p. 506).

Regulation of Glycolysis

- ATP/AMP ratios are important
- Two roles: energy production and building blocks for biosynthesis

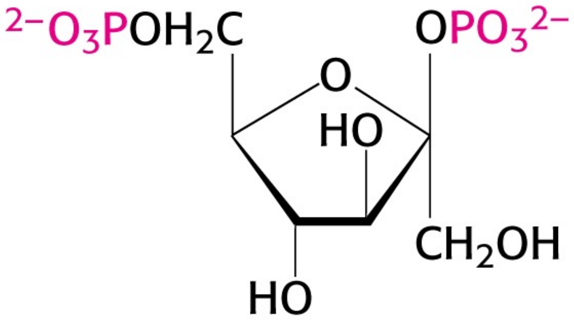


Regulation of Hexokinase

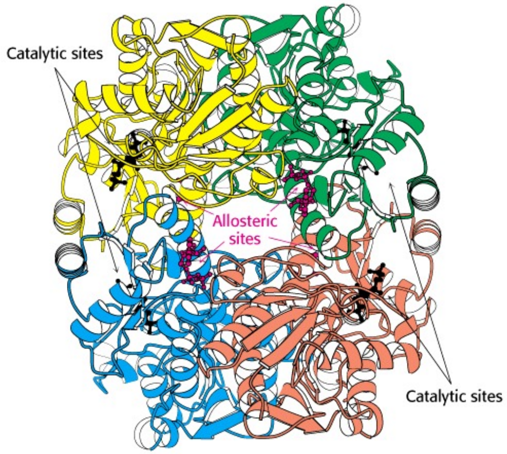


Phosphofructokinase: Highly regulated

- Allosteric enzyme:
- Activated by ADP and AMP
- Inhibited by ATP and Citrate (from TCA cycle)
- Fructose 2,6 bisphosphate regulation

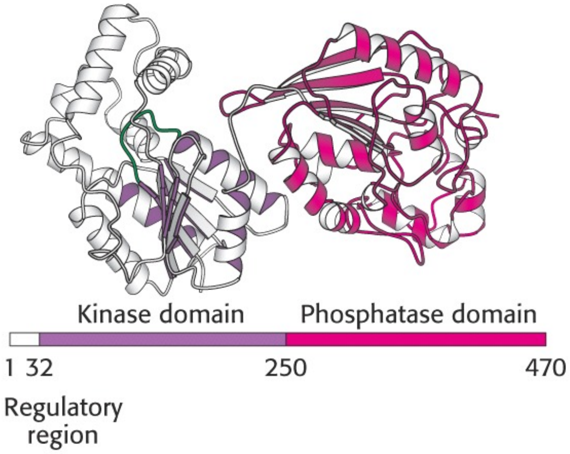


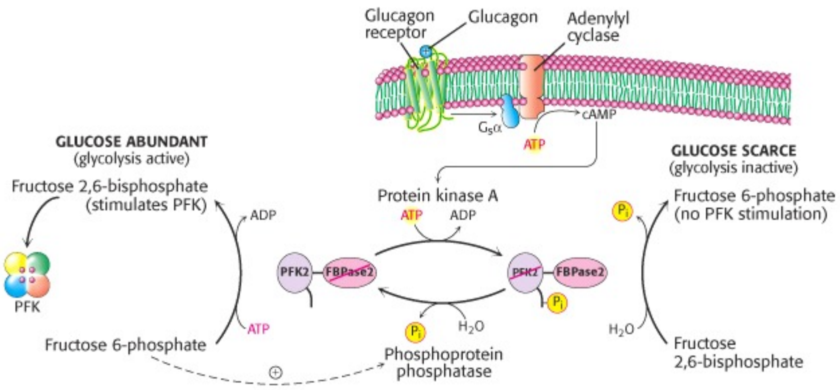
Fructose 2,6-bisphosphate (F-2,6-BP)



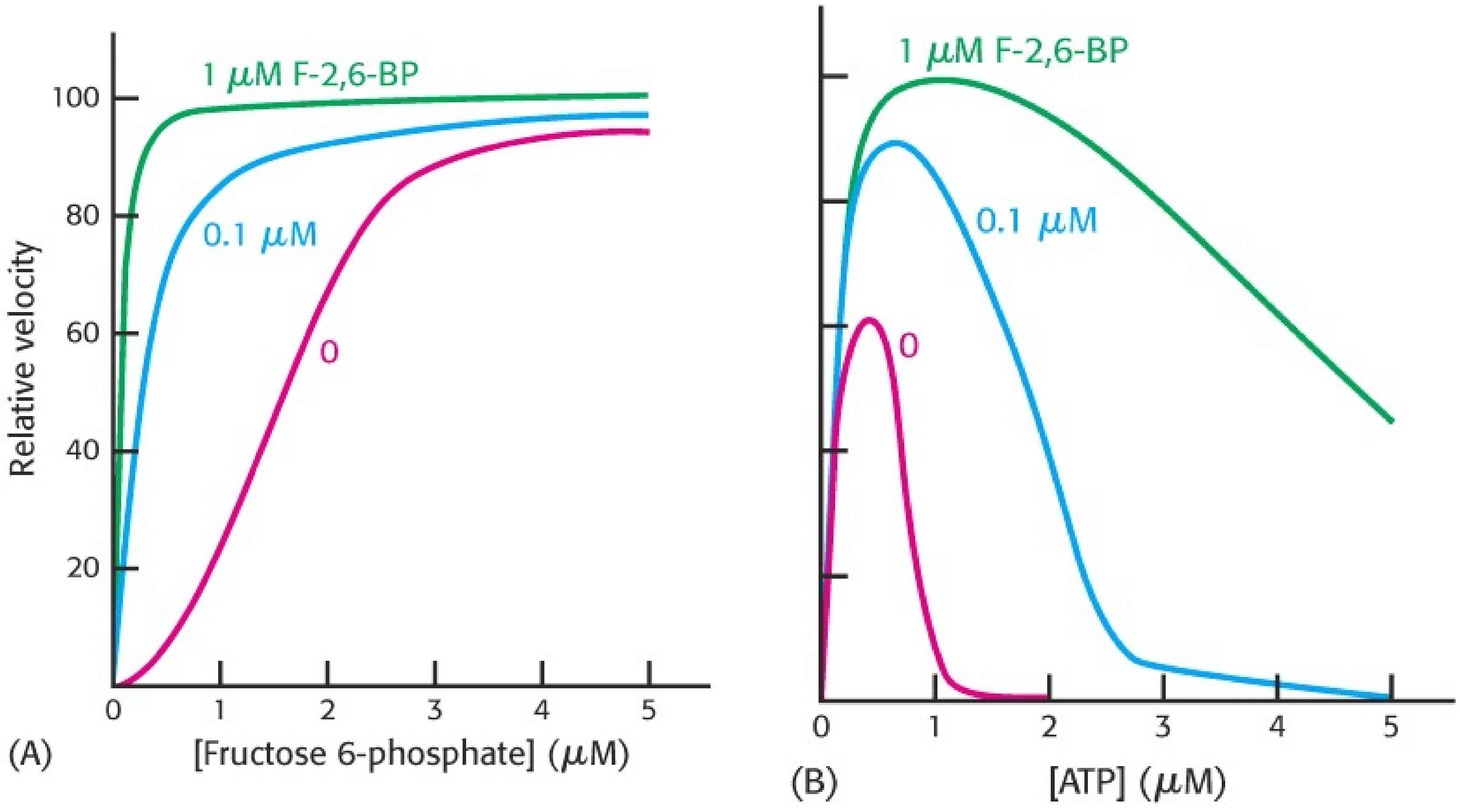
PFK-2

- **Tandem enzyme: PFK-2, both kinase and phsophotase together**
- **Fru 2,6 P potent activator of PFK-1**
- **prevents inhibition of citrate/ATP for fatty acid biosynthesis**
- **Relative velocity curves for PFK-1**
- **Effect of glucagon on PFK-1**





Activation of PFK-1 by Fru 2,6 Bis



Other sites of Regulation

- **Pyruvate kinase**
- **allosteric**
- **stimulated by fructose 1,6P**
- **inhibited by acetyl-CoA, fatty acids**
- **protein kinase inhibits pyruvate kinase**
- **Glyceraldehyde 3-P dehydrogenase**
- **stimulated by NAD+**